

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference NEREUS.183VPC	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/US2009/043644	International filing date (<i>day/month/year</i>) 12 May 2009	Priority date (<i>day/month/year</i>) 12 May 2008	
International Patent Classification (IPC) or national classification and IPC <div style="text-align: center;">Int. Cl.</div> <div style="display: flex; justify-content: space-around;"> C07D 491/044 (2006.01) A61K 31/655 (2006.01) A61P 31/04 (2006.01) </div> <div style="display: flex; justify-content: space-around;"> A61K 31/407 (2006.01) A61P 29/00 (2006.01) A61P 35/00 (2006.01) </div>			
Applicant NEREUS PHARMACEUTICALS, INC. et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p style="margin-left: 20px;">a. <input type="checkbox"/> (<i>sent to the applicant and to the International Bureau</i>) a total of sheets, as follows:</p> <div style="margin-left: 40px;"> <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. </div> <p style="margin-left: 20px;">b. <input type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3bis of Annex C of the Administrative Instructions).</p> <p>4. This report contains indications relating to the following items:</p> <div style="margin-left: 20px;"> <input checked="" type="checkbox"/> Box No. I Basis of the report <input checked="" type="checkbox"/> Box No. II Priority <input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application </div>			
Date of submission of the demand 12 March 2010		Date of completion of this report 06 August 2010	
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999		Authorized Officer Alicia Daly AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 3 9935 9606	

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/US2009/043644

Box No. I Basis of the report

1. With regard to the language, this report is based on:

- ☒ The international application in the language in which it was filed
- ☐ A translation of the international application into _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3(a) and 23.1 (b))
- ☐ publication of the international application (under Rule 12.4(a))
- ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on
- (replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

- ☒ the international application as originally filed/furnished
- ☐ the description:
- | | |
|--------|--|
| pages | as originally filed/furnished |
| pages* | received by this Authority on _____ with the letter of |
| pages* | received by this Authority on _____ with the letter of |
- ☐ the claims:
- | | |
|--------|---|
| pages | as originally filed/furnished |
| pages* | as amended (together with any statement) under Article 19 |
| pages* | received by this Authority on _____ with the letter of |
| pages* | received by this Authority on _____ with the letter of |
- ☐ the drawings:
- | | |
|--------|--|
| pages | as originally filed/furnished |
| pages* | received by this Authority on _____ with the letter of |
| pages* | received by this Authority on _____ with the letter of |

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

- 3.
- ☐
- The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:

- 4.
- ☐
- This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and
- (e-bis)*
-).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:

- 5.
- ☐
- This report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 70.2(e)).

- 6.
- ☐
- Supplementary international search report(s) from Authority(ies) _____ have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/US2009/043644

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
- ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

The priority document contains a valid disclosure of the invention which is the subject of the current application *in so far as* it relates to the subject matter that is disclosed in the prior published document, D4.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-138	YES
	Claims NONE	NO
Inventive step (IS)	Claims 1-138	YES
	Claims NONE	NO
Industrial applicability (IA)	Claims 1-138	YES
	Claims NONE	NO

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report. Full bibliographic details are provided in the International Search Report:

- D1 WO 2007/130404
 D2 Macherla et al. *J. Med. Chem.* 2005, 48(11), 3684-3687
 D3 Takashi et al. *Chemistry Letters* 1988, (11), 1877-1878
 D4 Manam et al. *J. Med. Chem.* 2008, 51(21), 6711-6724

The present claims define Salinosporamide derivatives of formula (I) that include a sulfonate ester, ester or ether group in the substituent at the 4-position of the 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione moiety. These derivatives can be included in pharmaceutical compositions and can be used as proteasome inhibitors for treating or ameliorating a disease or condition such as cancer, a microbial disease or inflammation.

Non-patent Literature P Category Documents

With regard to D4, this non-patent literature document discloses subject matter that is of particular relevance to this application. However, it was published after the priority date of the current application and under the PCT, only documents published before the priority date of the application being considered deprive the claims of that application of novelty. As the current application has a valid priority claim with regard to the subject matter disclosed in D4, it is not considered to be relevant in this opinion.

NOVELTY (N)

D1 discloses Salinosporamide analogues and methods of using them for the treatment of lung cancer (abstract).

D1 discloses an ethyl ester derivative (formula II-22, pp37 & 114) and a mesylate derivative (Formula II-41, pp45 & 118) of Salinosporamide A, which would be novelty destroying for the current claims except that the molecular weight of said substituents does not meet the proviso of claim 1. Therefore D1 is not relevant for novelty.

D2 discloses structure-activity relationships (SAR) of Salinosporamide derivatives (abstract). D2 does not disclose any compounds with a sulfonate ester, ester or ether group with the 4-position of the 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione moiety. Therefore D2 is not relevant for novelty.

D3 discloses fluorination reactions using silver fluoride supported on calcium fluoride. D3 is not relevant for novelty.

[continued in Supplemental Box]Error! Bookmark not defined.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: **Box V**

None of the citations disclose a compounds of Formula (I) of the current claims with a sulfonate ester, ester or ether group on the side chain that has a molecular weight over 92 g mol^{-1} for the sulfonate or 77 g mol^{-1} for the ester or ether; or a method for synthesising a compound of formula (B) using a silver reagent. Therefore the subject matter of claims 1 and 128 and their dependent claims is new and meets the requirements of Article 33(2) of the PCT with regard to novelty.